Cardiology in the Young

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Hypotension within 1 week of life associated with poor short- and long-term outcomes in very low birth weight infants

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Abstract

We examined whether hypotension in very low birth weight infants aged ⩽1 week was associated with hospital morbidities and overall mortality. Further, we studied whether hypotension was associated with poor neurodevelopmental outcomes in these patients at the corrected age of 18 months. A total of 166 very low birth weight infants were studied during this period. Hospital outcomes and neurodevelopmental outcomes at the corrected age of 18 months were evaluated. Among the 166 very low birth weight infants, 95 patients (57.2%) experienced hypotension at ⩽1 week and were associated with an increased incidence of morbidities and mortality. At the corrected age of 18 months, hypotension of the ⩽1 week group had significantly lower scores in all three – cognitive, language, and motor – composites of the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) screening tests. In addition, a multivariable logistic regression analysis showed that longer mechanical ventilation and periventricular leukomalacia were additionally associated with worse cognitive and language neurodevelopmental outcomes. Hypotension in very low birth weight infants within 1 week of life was associated with increased morbidities and overall mortality. It was also associated with an increased risk of cognitive and language outcomes.

Hypotension in very low birth weight infants is frequently observed in the neonatal ICU, with a reported incidence of up to 50%.[1–3] Many episodes of neonatal hypotension occur from unstable clinical conditions associated with prematurity; however, many are not able to be attributed to any identifiable causes and are thought to result idiopathically from immature cardiovascular regulation.[4] Its incidence is inversely related to gestational age, with an estimated incidence of up to 75% in infants born at less than 28 weeks' gestation.[2–5] Hypotension is associated with increased severity of intraventricular haemorrhage, poor long-term neurodevelopment, and even death.[6] In very low birth weight infants who were born weighing less than 1500 g, hypotension within the 1st week of life can be the first indication of a circulatory collapse, a condition that may require inotropic therapy or steroid treatment. Symptoms of hypotension within 1 week of life may be associated with other hospital morbidities in very low birth weight infants. The management of hypotension in very low birth weight infants varies because blood pressure limits without a physiologic basis, such as treating blood pressure below the 10th percentile for age or if the mean blood pressure is less than gestational age in weeks. Thus, significant variations in diagnosis, treatment, and approach persist. Our aim in this study was to evaluate whether very low birth weight infants who were diagnosed with systemic hypotension at ⩽1 week of life were at risk of increased hospital morbidities and mortality. Further, the long-term outcomes of very low birth weight infants diagnosed with hypotension at ⩽1 week of life were also assessed.

Methods

The clinical data for these infants relating to treatment modalities, hospital morbidities, and mortality were retrospectively collected for analysis. In our unit, we routinely follow-up very low birth weight infant up to corrected age of 18–24 months for neurodevelopmental assessments. At the corrected age of 18 months, surviving infants returned for follow-up evaluations and completed the cognitive, language, and motor components of the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) screening tests. At the corrected age of 18 months, patients were considered at risk if scores were >2 standard deviations (SDs) below the test mean (scores of < 70). The long-term data were also retrospectively chart-reviewed for analysis.

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To assess hypotension, blood pressure was measured directly with a transducer connected to an indwelling umbilical arterial catheter or noninvasively using oscillometric measurements. We defined systemic hypotension in very low birth weight infants as a mean blood pressure below the 3rd percentile for gestational age[7] or below 30 mmHg[8] with decreased urine output (<1 ml/kg/hour) for >12 hours. For very low birth weight infants who failed to maintain an adequate mean blood pressure with decreased urine output, fluid boluses – isotonic saline at a dose of 10 ml/kg per bolus – were given initially and could be repeated twice. Those who responded with only fluid boluses were not considered as having systemic hypotension at ⩽1 week of life and excluded. In addition, those who expired within a week of life were excluded from this study (Fig 1).

If the fluid boluses were unsuccessful in maintaining targeted mean blood pressure, they were diagnosed with systemic hypotension at ⩽1 week of life in this study. As an inotropic treatment, dopamine infusion was added. Dopamine infusions were started at a rate of 5 μg/kg/min and increased by 2.5 μg/kg/min until an adequate mean blood pressure – above the hypotensive range – was achieved. If 10 μg/kg/min dopamine failed to maintain an adequate mean blood pressure, dobutamine (10 μg/kg/min) was added.[7] If dopamine failed, hydrocortisone at a dose of 5 mg/kg/day IV, divided into three doses at 8-hour intervals, was added. Accordingly, patients with hypotension within 1 week of life treated with either inotropic therapy only or inotropics and a steroid were included in this study. Once patients maintained an adequate mean blood pressure with increased urine output, the inotropes were decreased at the same rate that they had been increased, and then hydrocortisone was tapered. Patients with hypotension that resulted in culture-positive infection, pneumothorax, massive pulmonary haemorrhage, and/or necrotising enterocolitis were excluded from this study. Idiopathic hypotension that had no identifiable cause other than prematurity was studied in relation to clinical outcomes. This study was approved by the Ethics Committee of Seoul St. Mary's Hospital, The Catholic University of Seoul, Korea.

Definitions

Systemic hypotension in very low birth weight infant was defined as a mean blood pressure below the 3rd percentile for gestational age[7] or below 30 mmHg[8] with decreased urine output (<1 ml/kg/hour) for >12 hours. Pulmonary hypertension is defined by the need for nitric oxide or sildenafil or iloprost treatment within 1 week of life. Infants were diagnosed with BPD if they required oxygen use exceeding 0.21% at a corrected gestational age of 36 weeks, at hospital discharge for those born before 32 weeks of gestational age, or at a postnatal age of 28–56 days for those born after 32 weeks of gestational age. Using Bell's classification, necrotising enterocolitis was defined as grade II or higher. On the basis of the classification criteria for intraventricular haemorrhage established by Papile and Levene, a grade greater than grade II was defined as active bleeding in the ventricles. Retinopathy of prematurity was defined as neovascular tufts found posterior to the ridge, and the classified determinations of higher than stage 3 were made according to the International Classification of Diseases for retinopathy of prematurity. At the corrected age of 18 months, patients were considered at risk if scores were >2 SDs below the test mean (scores of <70). The abnormal neurodevelopmental outcome was defined when scores of <70 in the areas of cognitive, language, or motor were found. The composite outcome was defined as death or abnormal neurodevelopmental outcome (scores of <70).

Statistical analysis

Continuous variables were compared using Student's t-test and are expressed as the means ± standard deviations. Discrete variables were compared using a χ^2 test or Fisher's exact test and are expressed as percentages. All of the analyses were two-tailed, and clinical significance was defined as a p-value lower than 0.05. To assess any confounding factors in relation to neurodevelopmental outcomes, we used a multivariate logistic regression analysis to identify any variables. Odds ratios and 95% confidence intervals were calculated using a multivariate statistical model that included the following variables related to neurodevelopmental outcomes in very low birth weight infants: hypotension ⩽1 week, gestational age, periventricular leukomalacia, and steroid use. Hosmer–Lemeshow goodness of fit test for interpretation of the model was performed as noted in Table 3. All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS), version 15.0 (SPSS-PC, Inc., Chicago, Illinois, United States of America).

Results

Demographic data

Between July 1, 2013 and October 1, 2015, a total of 206 very low birth weight infants were admitted to our neonatal ICU at Seoul St. Mary's Hospital (Fig 1). Of the 166 very low birth weight

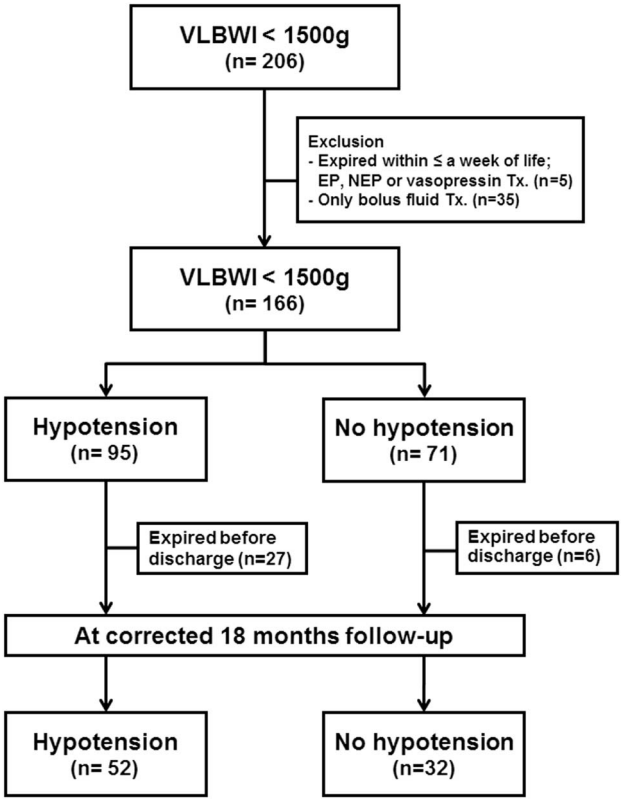

Figure 1. Nomogram of the study. VLBWI = very low birth weight infants; Tx = treatment.

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Table 1. Clinical characteristics of very low birth weight infants (n = 166); hypotension versus non-hypotension group

	Hypotension ⩽1 week (n = 95)	Non-hypotension (n = 71)	p-Value
Gestational age (weeks)	27.37 ± 2.29	29.03 ± 2.45	<0.001
Birth weight (g)	1061.81 ± 267.73	1134.94 ± 247.29	0.074
Male [n (%)]	53 (55.8)	30 (42.3)	0.084
Antenatal steroid use	63 (66.3)	40 (57.1)	0.229
PROM ⩾ 18 hours	36 (37.9)	31 (43.7)	0.454
Maternal chorioamnionitis	35 (40.2)	16 (25.8)	0.067
Resuscitation at delivery*	91 (96.8)	62 (91.2)	0.122
Intubation at delivery	83 (91.2)	46 (74.2)	0.004
Epinephrine use at delivery	15 (16.5)	2 (3.2)	0.010
RDS	91 (95.8)	62 (88.6)	0.078
Pulmonary hypertension**	16 (16.8)	5 (7.0)	0.060
Neonatal seizure	56 (58.9)	22 (31.0)	<0.001
PDA	26 (27.4)	13 (18.3)	0.173
Medical treatment***	12 (12.6)	6 (8.5)	0.391
Surgical treatment***	16 (16.8)	8 (11.3)	0.312
NEC operation	3/13 (37.5)	1/5 (20.0)	0.506
IVH > grade II	32 (38.6)	12 (17.1)	0.004
Hydrocephalus	17 (25.0)	6 (18.2)	0.443
Sepsis	45 (47.4)	20 (28.2)	0.012
ROP laser Tx	7 (7.4)	3 (4.2)	0.400
BPD ⩾ moderate	65 (87.8)	33 (49.3)	<0.001
Hospitalisation length (days)****	56.37 ± 35.60	49.03 ± 25.87	0.126
Mechanical ventilation (days)****	24.94 ± 24.18	13.32 ± 20.58	0.001
PVL	45 (54.2)	13 (18.8)	<0.001
Mortality	27 (28.4)	6 (8.5)	0.001

IVH = intraventricular haemorrhage; NEC = necrotising enterocolitis; PDA = patent ductus arteriosus; PROM = premature rupture of membrane; PVL = periventricular leukomalacia; RDS = respiratory distress syndrome; ROP = retinopathy of prematurity; Tx = treatment
*Resuscitation included oxygen use or positive pressure ventilation
**Use of nitric oxide, sildenafil, or iloprost within 1 week of birth
***Described as multiple answer
****Patients who died before discharge were excluded

infants, 95 (57.2%) were diagnosed with hypotension at ⩽1 week in the neonatal ICU of Seoul St. Mary's Hospital, The Catholic University of Korea (Fig 1). The mean gestational age was significantly lower in the hypotensive group. In addition, intubation and epinephrine use at delivery, and seizures, were significantly associated with hypotension at ⩽1 week ($p < 0.05$) (Table 1). In terms of morbidities, hypotension ⩽1 week was significantly related to intraventricular haemorrhage > grade II, sepsis, BPD ⩾ moderate, longer mechanical ventilation duration periventricular leukomalacia, and increased mortality ($p < 0.05$) (Table 1).

At the corrected age of 18 months, 33 patients died before discharge. Of the surviving very low birth weight infants, 84/133 (63.1%) returned for follow-up evaluations (Fig 1). They completed the cognitive, language, and motor components of the Bayley Scales of Infant and Toddler Development III. Those in the hypotension group had significantly lower composite scores for all three areas – cognitive, language, and motor – of Bayley Scales of Infant and Toddler Development III (Table 2). In addition, the hypotension group had a significantly higher prevalence of children at high risk, defined as a score > 2 SDs below the test mean (scores of <70). However, there was little evidence of differences in catch-up growth (Table 2).

To explore the influence of any possible confounding factors on long-term neurodevelopmental outcomes, we performed a multivariable logistic regression analysis to identify any confounding factors related to the cognitive, language, and motor composite scores on the Bayley Scales of Infant and Toddler Development III. In this analysis, we included gestational age, epinephrine use at delivery, mechanical ventilation, periventricular leukomalacia, and

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Table 2. Outcomes of surviving very low birth weight infant (VLBWI) on Bayley Scales of Infant and Toddler Development III at 18 months (n = 84)

	Hypotension ⩽1 week (n = 52)	No hypotension (n = 32)	p-Value
Score (mean ± SD)			
Cognitive	78.98 ± 21.77	91.50 ± 25.57	0.019
Language	78.69 ± 19.80	88.50 ± 23.09	0.042
Motor	73.62 ± 23.23	85.09 ± 25.03	0.036
At risk [n (%)]*			
Cognitive score	17 (32.7)	4 (12.5)	0.038
Language score	17 (32.7)	4 (12.5)	0.038
Motor score	23 (44.2)	7 (21.9)	0.038
Abnormal ND outcome**	28 (53.8)	8 (25.0)	0.009
Catch-up growth	53 (89.8)	49 (87.5)	0.693

ND = neurodevelopmental
*Children were considered to be at risk if their scores were >2 SD below the test mean (scores of <70)
**Abnormal ND outcome (scores of <70) of cognitive, language, or motor area

steroid use. In addition to hypotension at ⩽1 week, longer mechanical ventilation and periventricular leukomalacia were consistently associated with worse cognitive and language outcomes (Table 3).

Discussion

Hypotension is a common problem for very low birth weight infants in neonatal ICUs and may be regarded as an indicator of circulatory collapse and organ dysfunction. Kuint et al[9] reported that 66% of very low birth weight infants are treated for hypotension. Similarly, our study showed that 57.2% of very low birth weight infants were treated for hypotension at ⩽1 week of life. In our study, the hypotension was significantly related to unstable clinical factors such as resuscitation needed at delivery (Table 1). Some clinical factors may attribute to hypotension at ⩽1 week of life other than idiopathic hypotension originating from prematurity itself, but, consequently, very low birth weight infants who experienced hypotension requiring inotropics and steroid treatment had worse short- and long-term outcomes. These infants treated for systemic hypotension, a marker for haemodynamic instabilities, were more associated with adverse clinical morbidities, including intraventricular haemorrhage > grade II, sepsis, BPD ⩾ moderate, longer mechanical ventilation, periventricular leukomalacia, and mortality (Table 1). Other studies have similarly reported that these infants treated for hypotension developed periventricular leukomalacia and they were less likely to survive.[6,10] In addition to this finding, Faust et al[11] also showed that hypotension in very low birth weight infant within the first 24 hours of life may increase the incidence of BPD and a higher rate of death. The studies by Kuint et al[9] and Mizoguchi et al[12] additionally demonstrated that hypotension at ⩽24 hours of life increased the risk for PDA and the development of threshold retinopathy of prematurity, which was not apparent in our study. Moreover, hypotension has been identified as a predictor of inflammatory states, such as infection, necrotising enterocolitis, or following neonatal surgeries.[13]

Table 3. Risks for neurodevelopmental outcomes in multiple logistic regression analysis: effects on long-term outcome (adjusted for hypotension ⩽1 week, gestational age, epinephrine use at delivery, mechanical ventilation, periventricular leukomalacia (PVL), and steroid use)

	p-Value	OR	95% CI	H–L test (p-value)
Composite outcome*				0.775**
Hypotension ⩽1 week	0.011	3.527	1.335–9.321	
Gestational age (week)	0.335	0.904	0.735–1.110	
PVL	0.022	3.249	1.187–8.894	
Steroid use	0.249	1.928	0.632–5.882	
Cognitive				0.600**
Hypotension ⩽1 week	0.044	3.404	1.028–11.277	
Gestational age (week)	0.127	0.826	0.647–1.056	
PVL	0.015	4.781	1.357–16.840	
Steroid use	0.713	1.308	0.313–5.467	
Language				0.725**
Hypotension ⩽1 week	0.038	3.374	1.074–12.772	
Gestational age (week)	0.131	0.827	0.646–1.058	
PVL	0.004	7.316	1.897–28.207	
Steroid use	0.899	1.100	0.251–4.813	
Motor				0.704**
Hypotension ⩽1 week	0.041	2.832	1.041–7.707	
Gestational age (week)	0.463	0.925	0.752–1.138	
PVL	0.046	2.854	1.020–7.989	
Steroid use	0.397	1.653	0.516–5.290	

OR = odds ratio; CI = confidence intervals
*Death or abnormal neurodevelopmental outcome (scores of <70)
**H–L test: Hosmer–Lemeshow goodness of fit test (p > 0.05)

As described in our study, very low birth weight infants with hypotension at ⩽1 week of life showed poorer outcomes because they were initially sicker patients. This group required more delivery room resuscitation, and were started with a more complicated clinical course.

Regarding long-term neurodevelopmental outcomes, Batton et al[14] described a higher rate of poor neurodevelopmental outcomes, in addition to increased short-term complications, in infants with low blood pressure, regardless of treatment in a case–control study. Fanaroff et al also reported poorer neurodevelopmental outcomes[15] for these patients. Our study similarly observed that very low birth weight infants diagnosed with hypotension at ⩽1 week of life were significantly associated with worse neurodevelopmental outcomes. The association of systemic hypotension and poor neurodevelopment may have been related to cerebral under-perfusion, which may or may not have been clinically recognised. Low superior caval vein flow, a possible indicator of low cerebral blood flow, was reported to be associated with poor neurodevelopmental outcome.[16] Additional studies have supported that low blood pressure is correlated with poor cerebral blood flow.[17]

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Many preterm infants are unable to mount an appropriate cortisol response under stressful conditions.[18] This is especially a factor in preterm infants before 27 weeks, who are reported to have lower serum cortisol levels compared with adults.[19] Our study also manifested that very low birth weight infants experiencing more hypotension ⩽1 week of life had significantly lower gestational age (27.37 ± 2.29 versus 29.03 ± 2.45). Although some infants develop hypotension secondary to maladaptation of a sudden change in loading conditions, it is possible that in more premature infants a relative adrenal insufficiency may play a more dominant role. Low serum cortisol levels and an association with adverse outcomes have highlighted the relative adrenal insufficiency in some sick preterm infants.[20–21] As a result of this condition, vasopressor-resistant hypotension that is responsive to hydrocortisone can be commonly seen in more sick preterm and neonatal babies.[22–23] Hypotension that cannot be managed only by inotropics but requires further steroid use, either as an anti-inflammatory or to elevate cortisol response under stressful conditions, may suggest additional worse clinical conditions that can result in worse hospital outcomes, such as the longer mechanical ventilation and higher mortality shown in our study (Table 2). The underlying disadvantages associated with more prematurely born infants who also experienced more chorioamnionitis might additionally result in worse neurodevelopmental outcomes in the hypotension group who received more steroids. Accordingly, hypotension within 1 week of life suggests that close follow-up for long-term neurodevelopmental outcomes is necessary for very low birth weight infants. Some limitations of our study are as follows: the retrospective study design, which may not be the proper way to confirm the examined relationships; the relatively small sample size of the study groups, which reduces this study's power; and the complex clinical conditions and co-morbidities may result hypotension other than originating from the condition of prematurity itself may act as confounding variables in this study. Hypotension within 1 week of life was associated with other morbidities and increased mortality. Our results suggest that hypotension ⩽1 week in very low birth weight infants may increase the risk for poor neurodevelopmental outcomes. Prematurity-related risks may also be considered as risk factors for poor neurodevelopmental outcomes.

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Conflicts of Interest. None.

References

1. Gill AB, Weindling AM. Randomised controlled trial of plasma protein fraction versus dopamine in hypotensive very low birthweight infants. Arch Dis Child 1993; 69: 284–287.
2. Seri I, Evans J. Controversies in the diagnosis and management of hypotension in the newborn infant. Curr Opin Pediatr 2001; 13: 116–123.
3. Barrington KJ, Dempsey EM. Cardiovascular support in the preterm: treatments in search of indications. J Pediatr 2006; 148: 289–291.
4. Noori S, Seri I. Pathophysiology of newborn hypotension outside the transitional period. Early Hum Dev 2005; 81: 399–404.
5. Al-Aweel I, Pursley DM, Rubin LP, Shah B, Weisberger S, Richardson DK. Variations in prevalence of hypotension, hypertension, and vasopressor use in neonatal ICUs. J Perinatol 2001; 21: 272–278.
6. name>Fanaroff JM, Wilson-Costello DE, Newman NS, Montpetite MM, Fanaroff AA. Treated hypotension is associated with neonatal morbidity and hearing loss in extremely low birth weight infants. Pediatrics 2006; 117: 1131–1135.
7. Zubrow AB, Hulman S, Kushner H, Falkner B. Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. Philadelphia Neonatal Blood Pressure Study Group. J Perinatol 1995; 15: 470–479.
8. Joint Working Group of the British Association of Perinatal Medicine and the Research Unit of the Royal College of Physicians. Development of audit measures and guidelines for good practice in the management of neonatal respiratory distress syndrome. Arch Dis Child 1992; 67: 1221–1227.
9. Kuint J, Barak M, Morag I, Maayan-Metzger A. Early treated hypotension and outcome in very low birth weight infants. Neonatology 2009; 95: 311–316.
10. Synnes AR, Chien LY, Peliowski A, Baboolal R, Lee SK, Canadian NICU Network. Variations in intraventricular hemorrhage incidence rates among Canadian neonatal intensive care units. J Pediatr 2001; 138: 525–531.
11. Faust K, Hartel C, Preuss M, et al. Short-term outcome of very-low-birthweight infants with arterial hypotension in the first 24 h of life. Arch Dis Child Fetal Neonatal Ed 2015; 100: F388–F392.
12. Mizoguchi MB, Chu TG, Murphy FM, Willits N, Morse LS. Dopamine use is an indicator for the development of threshold retinopathy of prematurity. Br J Ophthalmol 1999; 83: 425–428.
13. McNamara PJ, Stewart L, Shivananda SP, Stephens D, Sehgal A. Patent ductus arteriosus ligation is associated with impaired left ventricular systolic performance in premature infants weighing less than 1000 g. J Thorac Cardiovasc Surg 2010; 140: 150–157.
14. Batton B, Zhu X, Fanaroff J, et al. Blood pressure, anti-hypotensive therapy, and neurodevelopment in extremely preterm infants. J Pediatr 2009; 154: 351–357, 357.e351.
15. Fanaroff AA, Fanaroff JM. Short- and long-term consequences of hypotension in ELBW infants. Semin Perinatol 2006; 30: 151–155.
16. Hunt RW, Evans N, Rieger I, Kluckow M. Low superior vena cava flow and neurodevelopment at 3 years in very preterm infants. J Pediatr 2004; 145: 588–592.
17. Tyszczuk L, Meek J, Elwell C, Wyatt JS. Cerebral blood flow is independent of mean arterial blood pressure in preterm infants undergoing intensive care. Pediatrics 1998; 102: 337–341.
18. Hingre RV, Gross SJ, Hingre KS, Mayes DM, Richman RA. Adrenal steroidogenesis in very low birth weight preterm infants. J Clin Endocrinol Metab 1994; 78: 266–270.
19. Scott SM, Watterberg KL. Effect of gestational age, postnatal age, and illness on plasma cortisol concentrations in premature infants. Pediatr Res 1995; 37: 112–116.
20. Huysman MW, Hokken-Koelega AC, De Ridder MA, Sauer PJ. Adrenal function in sick very preterm infants. Pediatr Res 2000; 48: 629–633.
21. Watterberg KL, Scott SM, Backstrom C, Gifford KL, Cook KL. Links between early adrenal function and respiratory outcome in preterm infants: airway inflammation and patent ductus arteriosus. Pediatrics 2000; 105: 320–324.
22. Helbock HJ, Insoft RM, Conte FA. Glucocorticoid-responsive hypotension in extremely low birth weight newborns. Pediatrics 1993; 92: 715–717.
23. Ng PC, Lee CH, Bnur FL, et al. A double-blind, randomized, controlled study of a "stress dose" of hydrocortisone for rescue treatment of refractory hypotension in preterm infants. Pediatrics 2006; 117: 367–375.